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| EXAMINER | |
|---|---|
| GABEL, GAILENE | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/780,399 | RAO ET AL. | |
| | Examiner | Art Unit | |
| | GAILENE R. GABEL | 1641 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 December 2008 and 03 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *44-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Amendment Entry*

1. Applicant's amendment and response filed December 2, 2008 and February 3, 2009 are acknowledged and have been entered. Claims 44 and 53 have been amended. Currently, claims 44-61 are pending and are under examination.

### *Withdrawn Rejections / Objections*

2. All rejections or objections not reiterated herein, have been withdrawn.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 44-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 44, step d) as amended, is confusing in reciting, "analyzing... over time, a change in the presence of said labeled malignant cells" because it is unclear how "presence" is changed and what is encompassed in reciting, "over time" as used in the claim. It appears that "presence" can only be changed into "absence." Hence, does Applicant intend that over time, there is repetitive analysis of the sample, and the occurrence of malignant cells, cell fragments, and cell debris in the sample become

present and absent between analysis? Does Applicant perhaps intend, that more than one biological sample(s) are obtained from the test subject, and that each sample is analyzed using the claimed method, and then a change in the amount of labeled malignant cells, labeled cell fragments, and labeled cell debris, individually and separately provide a monitor of malignancy in a test subject? Please clarify.

Claim 53, step c) lacks antecedent basis in reciting, "said... cell fragments and said cellular debris" because steps a) and b) recite "malignant cells and clusters of malignant cells."

Claim 53, step d) as amended, is confusing in reciting, "analyzing... over time, a change in the presence of said labeled malignant cells" because it is unclear how "presence" is changed and what is encompassed in reciting, "over time" as used in the claim. It appears that "presence" can only be changed into "absence." Hence, does Applicant intend that over time, there is repetitive analysis of the sample, and the occurrence of malignant cells and malignant cell clusters in the sample become present and absent between analysis? Does Applicant perhaps intend, that more than one biological sample(s) are obtained from the test subject, and that each sample is analyzed using the claimed method, and then a change in the amount of labeled malignant cells and malignant cell clusters, individually and separately provide a monitor of malignancy in a test subject? Please clarify.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 44-61 are rejected under 35 U.S.C. 102(e) as being anticipated by Schmitz et al. (US Patent 6,190,870) for reasons of record.

Schmitz et al. disclose an efficient enrichment and detection method and kit for detecting disseminated malignant cells in peripheral blood sample comprising a mixed cell population suspected of containing malignant cells (Abstract, col. 1, lines 33-46, col. 2, lines 1-21, and col. 9, lines 43-59). The cells are distant from their site of primary tumor, and their presence amongst hematopoietic blood cells is indicative of malignancy (metastatic potential) of the tumor or carcinoma cells (col. 1, lines 35-38). The blood sample is treated with stabilizing agent (fixative) prior to performing the enrichment method (col. 1, lines 38-40 and col. 6, line 44 to col. 7, line 4). In practice, the blood sample is mixed with colloidal magnetic particles having specific antibodies coated thereto, that specifically bind a first determinant, i.e. cytokeratin, present in malignant cells (column 5, lines 29-41, col. 7, lines 5-22, and col. 8, lines 11-14). The malignant cells comprise cell surface antigens or determinants which are separation markers upon which the antibody-coated magnetic particles specifically bind or react to (col. 2, lines 33-60). The coated magnetic particles are nanoparticles comprising of a core material

(magnetic iron-dextran), protein base polymeric coating (biotin, avidin), and antibody that binds to a characteristic determinant of a malignant cell. The size of the magnetic particles are within the range of 10 nm to 100 nm (col. 5, lines 42-67). The sample having magnetically labeled malignant cells are subjected to high gradient magnetic field to produce separated and enriched malignant cell populations (col. 5, lines 15-19 and lines 49-52, and col. 7, lines 23-64). The cell mixture is further contacted with specific antibodies conjugated to a detectable label that specifically bind a second determinant present in malignant cells. Reagent labels may include a specific agent capable of labeling non-target entities (blocking agent that reduce non-specific labeling). The detectable labels may comprise a panel (cocktail) of antibodies specific for different malignant cell determinants (col. 6, lines 10-35). Thereafter, the antibody-coated magnetic particle – malignant cell – antibody label complexes are analyzed for the presence of labeled malignant cells, the presence of which provides indication of the presence of malignancy. Analysis of the presence of malignant cells complexed with magnetic particles and detectable labels are performed using flow cytometry, manual cell microscopic analysis, and fluorescent immunocytochemistry microscopic analysis (col. 6, lines 36-43). See also Examples 1-3. The malignant cells may further be characterized as to their phenotype using PCR, ELISA, FISH, chromosome painting, and immunocytochemistry (col. 9, lines 4-15).

In as far as cell fragments, cell debris, and cell clusters amongst malignant cells, it appears that so long as the conserved determinants or cell surface epitopes are present and maintained in the fragments, debris, or clusters in the cell sample along

with the malignant cells, for binding to antibody-coated magnetic particles and antibody-conjugated detectable labels that are specific for the desired conserved epitope common to all intact malignant cells, cell fragments, cell debris, and cell clusters, it would appear that all of the intact malignant cells, cell fragments, cell debris, and malignant cell clusters will be detected and analyzed as to their presence and characterization to provide indication of the presence of malignancy in a cell sample.

In as far as claims 50-52, Schmitz et al. provide phenotypic characterization of the malignant cells according to fragment length polymorphisms and presence or absence of specific sequences using PCR, ELISA, FISH, and immunocytochemistry (col. 9, lines 4-43).

5. Claims 44-46, 48, 49, 53-55, and 57-61 are rejected under 35 U.S.C. 102(e) as being anticipated by Fodstad et al. (US Patent 6,265,229) for reasons of record.

Fodstad et al. disclose an enrichment and detection method and kit for detecting disseminated malignant cells in peripheral blood sample comprising a mixed cell population suspected of containing malignant cells. The staging of disease with regards to whether it is localized or metastatic spread has occurred to other tissues, is of utmost important (Abstract, col. 4, lines 12-19, and co. 9, line 57 to col. 10, line 22). In practice, the blood sample is mixed with paramagnetic particles having specific antibodies coated thereto, that specifically bind a first determinant (cell surface antigen) present in malignant cells. The sample having magnetically labeled malignant cells are subjected to high gradient magnetic field to produce separated and enriched malignant cell

populations (col. 5, line 57 to col. 6, line 54). The blood sample may be treated with stabilizing agent (fixative) prior to or after performing the enrichment method. The malignant cells comprise cell surface antigens or determinants upon which the antibody-coated magnetic particles specifically bind or react to (col. 5, lines 13-37). The cell mixture is further contacted with specific antibodies conjugated with a detectable label that specifically bind a second determinant present in malignant cells (col. 8, lines 14-26). The antibody-coated magnetic particle – malignant cell – antibody label complexes are analyzed for the presence of labeled malignant cells, the presence of which provides indication of the presence of malignancy. Analysis of the presence of malignant cells complexed with magnetic particles and detectable labels are performed using microscopic analysis, PCR, and immunocytochemistry (claims 1, 9-13, and 20).

In as far as cell fragments, cell debris, and cell clusters amongst malignant cells, it appears that so long as the conserved determinants or cell surface epitopes are present and maintained in the fragments, debris, or clusters in the cell sample along with the malignant cells, for binding to monoclonal antibody-coated magnetic particles and antibody-conjugated detectable label that are specific for the desired conserved epitope common to all intact malignant cells, cell fragments, cell debris, and cell clusters, it would appear that all of the intact malignant cells, cell fragments, cell debris, and malignant cell clusters will be detected and analyzed as to their presence and characterization to provide indication of the presence of malignancy in a cell sample.

***Response to Arguments***

6. Applicant's arguments filed December 2, 2008 have been fully considered but they are not persuasive.

A) Applicant argues that Schmitz et al. does not anticipate the claimed invention because the reference relies on high gradient magnetic separation using internal magnet coupled with the use of density gradients for separation of intact target cells. Applicant contends that Schmitz et al. requires use of ferromagnetic matrix followed by flow cytometric enumeration. Applicant then argues that Schmitz et al. does not discuss or appreciate additional considerations in the combined analysis of malignant cells, debris, fragments and malignant cell clusters.

In response, Applicant's argument is not persuasive because the claimed method does not appear to exclude use of high gradient magnetic separation using internal magnet and use of density gradients. Specifically, independent claims 44 and 53 recite the "comprising" transition language. "The transition comprising' in a method claim indicates that the claim is open-ended and allows for additional steps."); Genentech, Inc. v. Chiron Corp., 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.); Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts").

Applicant's argument is further not persuasive because claims 44 and 53 broadly recite, "preparing... wherein the biological sample is mixed with magnetic particles coupled to a first biospecific ligand..., to the substantial exclusion of other specimen components when the sample is exposed to an externally-applied magnetic field" and fail to clearly define a positive and active step of exposing the sample to externally-applied magnetic field in the claimed method. The claimed invention further does not exclude use of paramagnetic particles formed from ferromagnetic matrix as taught by Schmitz et al.. Claims 44 and 53 broadly recite magnetically labeling the cells using magnetic particles and fail to clearly recite and define how Applicant's magnetic particles are distinct from the ferromagnetic particles of Schmitz et al. The claimed invention also recites use of flow cytometric analysis in claims 49 and 58 which is consonant to the teaching of Schmitz et al. on flow cytometric enumeration of the target cells.

In response to Applicant 's argument that Schmitz et al. does not discuss or appreciate additional considerations in the combined analysis of cells, debris, and fragments, although cellular fragments from malignant cells and cellular debris from malignant cells are recited to comprise the biological sample, it appears that occurrence of the same components should inherently be present in the biological sample taught by Schmitz et al. as in the case of malignancy. It is, therefore, maintained that antibodies as taught by Schmitz et al. that bind defined conserved epitopes or determinants present in the malignant cells would also bind the same epitopes or determinants present and retained in the cell fragments or cell derivatives, and will be detected and

analyzed as to their presence and characterization to provide indication of the presence of malignancy in a cell sample.

Applicant's arguments are not persuasive because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references.

B) Applicant argues that Fodstad et al. does not anticipate the claimed invention because the reference does not discuss or appreciate additional considerations in the combined analysis of cells, debris, and fragments. Artifacts from damaged CTC in processing and other artifactual considerations not appreciated or discussed in Fodstad et al. would inhibit effective analysis of intact malignant cells, cell fragments, cell debris, and malignant cell clusters.

In response, Applicant's argument is not persuasive because the claimed method does not appear to exclude the magnetic separation method as taught by Fodstad et al. Specifically, independent claims 44 and 53 recite the "comprising" transition language. "The transition comprising' in a method claim indicates that the claim is open-ended and allows for additional steps."); Genentech, Inc. v. Chiron Corp., 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) ("Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.); Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); Ex parte Davis, 80 USPQ 448, 450

(Bd. App. 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts").

Applicant's argument is further not persuasive because claims 44 and 53 broadly recite, "preparing... wherein the biological sample is mixed with magnetic particles coupled to a first biospecific ligand..., to the substantial exclusion of other specimen components when the sample is exposed to an externally-applied magnetic field" and fails to clearly define a positive and active step of exposing the sample to externally-applied magnetic field in the claimed method. Claims 44 and 53 broadly recite magnetically labeling the cells using magnetic particles and fails to clearly recite and define how Applicant's magnetic particles are distinct from the paramagnetic particles of Fodstad et al.

In response to Applicant 's argument that Fodstad et al. does not discuss or appreciate additional considerations in the combined analysis of cells, debris, and fragments, although cellular fragments from malignant cells and cellular debris from malignant cells are recited to comprise the biological sample, it appears that occurrence of the same components should inherently be present in the biological sample taught by Fodstad et al. as in the case of malignancy. It is, therefore, maintained that antibodies as taught by Fodstad et al. that bind defined conserved epitopes or determinants present in the malignant cells would also bind the same epitopes or determinants present and retained in the cell fragments or cell derivatives, and will be detected and analyzed as to their presence and characterization to provide indication of the presence of malignancy in a cell sample.

Applicant's arguments are not persuasive because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references.

7. No claims are allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GAILENE R. GABEL whose telephone number is

(571)272-0820. The examiner can normally be reached on Monday, Tuesday, Thursday, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark L. Shibuya can be reached on (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/GAILENE R. GABEL/
Primary Examiner, Art Unit 1641

April 29, 2009